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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/214,251	03/10/1999	DAVID JOHN KING	CARP-0067	9023

7590 10/30/2002

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EXAMINER	
HELMS, LARRY RONALD	
ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 10/30/2002

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/214,251	Applicant(s) KING ET AL.	
	Examiner Larry R. Helms	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *9/19/02* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5 and 9-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5 and 9-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 5, 9-19 are pending.

Claims 9 and 12 have been amended.

Claims 13-19 have been added.

2. Claims 5 and 9-19 are under examination.

3. The text of those sections of Title 35 U.S.C. code not included in this office action can be found in a prior Office Action

4. The following Office Action contains some NEW GROUNDS of rejection.

Rejections Withdrawn

5. The rejection of claims 9-12 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of the amendments to the claims.

Response to Arguments

6. The rejection of claims 5, 11 and 12 under 35 U.S.C. 102(b) as being anticipated by Zapata et al (FASEB J. 9:A1479, 1995) is maintained.

The response filed 9/19/02 has been carefully considured but is deemed not to be persuasive. The response states "The Zapata I reference does not teach that the cysteine residue that forms a portion of a single free thiol is the only cysteine residue in

the hinge region" and "merely because Zapata I reference reports that the antibody recited therein contains a single free thiol does not mean that the cysteine residue that forms a portion of the single free thiol is the only cysteine residue in the hinge region" (see page 4 of response). In response to this argument, Zapata teach that the Fab' contains a single cysteine residue and the polymer is attached to the sulfhydryl group in the hinge. Thus if the antibody only contains one thiol and the polymer is attached to a cysteine residue, it is inherent that the polymer is attached to the only cysteine in the hinge region.

7. The rejection of claims 5, 9-12 and newly added claims 13-17 and 19 under 35 U.S.C. 103(a) as being unpatentable over Zapata et al [a] (FASEB J. 9:A1479, 1995) as applied to claims 5, 11-12 above, and further in view of Zapata [b] (U. S. Patent 6,214,984, continuation date of 4/20/95) is maintained and made again.

The response filed 9/19/02 has been carefully considured but is deemed not to be persuasive. The response states the "Zapata II reference does not teach that the cysteine residue that forms a portion of the single free thiol is the only cysteine residue in the hinge region domain" and Column 17 discloses that the humanized anti-CD18 Fab' was prepared from SEQ ID NO:1 and 2 and SEQ ID NO:2 which is a heavy chain sequence does not contain hinge region and a cysteine in the hinge region (see pages 5-6 of response). In response to these arguments, the Zapata I reference teaches the polymer attached to a single hinge cysteine as discussed above. The Zapata II reference does teach as stated in the response that the Fab' was produced from SEQ

ID NO:1 and 2, however, it is not clear if SEQ ID NO:2 comprises the Variable domain and a CH1 domain, however, as stated in Zapata II the Fab' was engineered to contain a free thiol in the hinge (see column 17, lines 35-45). The hinge sequence was obviously from the vector sequence as stated in Zapata II where the SEQ ID NO:1 and SEQ ID NO:2 were cloned into (see column 17, lines 10-25). In addition, the Zapata II Fab obviously contains a single free thiol in the hinge because Zapata II teach adding 4,4-DTP to protect the free cysteine in the Fab' (see column 17, lines 39-43). In addition, since the antibody is humanized it would obviously have the CDRs from a mouse antibody and the rest of the variable domain of a human antibody.

8. The rejection of claims 5, 9-12 and newly added claims 13-17 under 35 U.S.C. 103(a) as being unpatentable over Jacobs et al (U. S. Patent 5,853,723, filed 9/20/96) and further in view of Bodmer et al (WO 89/01974, published 3/9/89) is maintained and made again.

The response filed 9/19/02 has been carefully considured but is deemed not to be persuasive. The response states that the advantage of Bodmer is stated by the Office to be reducing the number of cysteine in the hinge to 1 that will facilitate assembly of the antibody molecule, however, this is not applicable because applicants claims are directed to polymer modified monovalent antibody fragments and Jacobs teaches attaching effectors or reporters to the hinge region and the cysteine of Jacobs would not be available for attachment (see page 7 of response). In response to these arguments, Jacobs clearly teaches monovalent fragments of Fab' with attachments of

polymers to the hinge cysteine and this does not require assembly to a divalent molecule and in view of Bodmer who teaches reduction of the hinge cysteines to one and attaching an effector which can be a polymer to the one cysteine residue it would have been obvious to reduce the hinge cysteines to one and attach a polymer to the cysteine.

The following are some NEW GROUNDS of rejections

Claim Rejections - 35 USC § 112

9. Claim 17 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 17 recites the limitation "the soluble antigen" in claim 19. There is insufficient antecedent basis for this limitation in the claim.

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claim 19 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a polymer modified antibody fragment where in the antibody comprises all six CDRs from one antibody and the framework from another

antibody wherein the antibody fragment binds antigen, does not reasonably provide enablement for a fragment of an antibody that does not comprise a full set of six CDRs from one antibody and framework regions from a second antibody. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claim encompasses an antibody fragment with only one CDR from one antibody and the rest of the variable domain including the other CDRs from another antibody. The specification teaches several antibodies that bind antigen and have a full set of CDRs for binding. The specification does not enable an antibody that binds antigen which comprises only one CDR from one antibody and the framework and the other CDRs from another.

It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The

amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc Natl Acad Sci USA 1982 Vol 79 page 1979, PTO-892, Part of Paper #5). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. It is unlikely that fusion proteins as defined by the claims which may contain less than the full complement of CDRs from the heavy and light chain variable regions of an IL-1ß antibody in unspecified order and fused to any human or nonhuman framework sequence, have the required binding function. The specification provides no direction or guidance regarding how to produce antibodies as broadly defined by the claims.

Therefore, in view of the unpredictability in the art and in view of the lack of guidance in the specification and in view of the broadly claimed invention, undue experimentation would be required to practice the invention commensurate with the scope of the claims.

Claim Rejections - 35 USC § 103

14. Claims 5, 9-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zapata et al [a] (FASEB J. 9:A1479, 1995), and further in view of Zapata [b] (U. S. Patent 6,214,984, continuation date of 4/20/95) and Faanes et al (U.S. Patent 5,695,760, filed 4/95).

Zapata et al [a] teach a Fab' fragment which contains a single cysteine in the hinge region and coupling of monomethoxypoly(ethylene glycol) to the cysteine and the mePEG-Fab' with the 10 kDa had reduced clearance compared to the 5 kDa modified species. Zapata et al [a] does not specifically teach a composition with a carrier or a fragment with an effector or reporter molecule or the polymer has an average molecular weight of 25 to 40 kDa or the fragment is a humanized antibody. These deficiencies are made up for in the teachings of Zapata [b] and Faanes et al.

Zapata [b] teach a Fab' fragment that has been engineered to have one cysteine in the hinge (see column 17, lines 35-43) and the antibody fragment can be labeled with a reporter molecule (see column 14, lines 29-37) and compositions comprising carriers (see column 15, lines 9-36) and humanized forms of the antibody (see column 5, lines 18-49).

Faanes et al teach the methods and modifications of antibodies with attachment of PEG molecules to the antigen binding fragments. Faanes et al teach humanization (column 14, line 40), fragments of the antibody (Fab and F(ab')2) (see column 10, lines 12-13), derivatives of PEG (column 12, lines 19-28), antibodies with biological excipient

(column 19, lines 49-57) which are sterile (column 20, line 20), and the antibodies can be modified to contain about 2-15 molecules of PEG (column 6, lines 21-24) with PEG 5 kD to up to 40 kDa higher molecular weight PEGs (column 12, lines 60-65, column 14, lines 9-10).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have used the antigen binding fragment with PEG as taught by Zapata et al [a] and label the fragment and produce compositions comprising a carrier and the antibody as taught by Zapata [b] and use the PEG which has a molecular weight of 40 kDa as taught by Faanes et al.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have used the antigen binding fragment with PEG as taught by Zapata et al [a] and label the fragment and produce compositions comprising a carrier and the antibody as taught by Zapata [b] and use the PEG which has a molecular weight of 40 kDa as taught by Faanes et al because Zapata et al [a] teach "the ability to modify the clearance rate of an antibody Fab' fragment by attaching a single MePEG moiety at a unique site, without affecting antigen binding, increases significantly the potential therapeutic value of this type of molecule" and the 10 kDa derivative had better clearance rates than the 5 kDa modified fragment. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have used the antigen binding fragment with PEG as taught by Zapata et al [a] and label the fragment and produce compositions comprising a carrier and the antibody as taught by Zapata [b] and use the PEG which has a

molecular weight of 40 kDa as taught by Faanes et al because Zapata [b] teach therapeutic applications for CD18 with anti-CD18 antibody fragments and these fragments can be labeled with a detectable moiety and the antibodies can be used in therapeutic applications when combined with acceptable carriers (see column 14 and column 15). In addition, it would have been obvious to one of skill in the art to label antibody fragments for detection or therapy and to formulate compositions comprising a carrier for therapeutic applications. Moreover, it would have been obvious to use the 40 kDa PEG in view of Zapata et al [a] showing higher molecular weight of 10 kDa compared to 5 kDa resulted I better clearance and Faanes et al teach using PEG up to 40 kDa.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusions

15. No claims are allowed.

16. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (703) 306-5879. The examiner can normally be reached on Monday through Friday from 7:00 am to 4:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

18. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 308-4242.

Respectfully,

Larry R. Helms Ph.D.

703-306-5879

Sheela G. Huff

SHEELA HUFF
PRIMARY EXAMINER